Acta Myologica • 2009; XXVIII: p. 12-15

# Collaborating to bring new therapies to the patient - the TREAT-NMD model

K. Bushby, S. Lynn, V. Straub on behalf of the TREAT-NMD network

*Institute of Human Genetics, University of Newcastle, International Centre for Life, Newcastle upon Tyne, England*

## 1. The overall aims of TREAT-NMD

TREAT-NMD is a European neuromuscular network awarded by the European Commission (contract number EC 036825) following successful lobbying efforts by groups such as the AFM and ENMC to address the fragmentation currently hindering translational research for cutting edge therapies in rare neuromuscular diseases (NMD). By bringing together experts from different European centres (Table 1) and working with teams from across the world, it is aiming to accelerate the clinical application of promising treatments for rare NMD. Bringing promising cutting edge therapies into clinical settings is currently delayed by the lack of standardised protocols for preclinical animal studies, molecular diagnoses and patient assessment and management. TREAT-NMD is addressing this fragmentation by establishing a common road map for the progression of cutting edge therapies from laboratory to clinic, from the assessment of cellular and animal models, via issues of delivery, production and toxicology, to relevant clinical outcome measures. This is underpinned by the integration and establishment of pan-European patient databases and biobanks and their global extension. The TREAT-NMD Coordination Centre (TNCC) is developing and integrating organisations and networks comprising the top researchers, clinicians and industries working in Europe in partnership with patient organisations in order to deliver the dream of treatments for these devastating disorders. Technological, educational and communication resources (*www.treat-nmd.eu*) have been developed as a durable resource co-ordinated by the TNCC. A strong educational programme will also provide the next generation of experts with the necessary background and expertise to maintain this leading position, and integrate the voices of patient organisations in the development of future research plans. Cutting edge treatments currently under development for muscular dystrophies and spinal muscular atrophy have been specifically targeted in this process, while future developments for other disease groups have been benefiting from the durable infrastructure of the TNCC, which will act as the portal for future pharmaceutical developments in the neuromuscular field.

Knowledge of disease causing genes has begun to allow the elucidation of the molecular pathological mechanisms underlying NMDs, leading to plans for specific gene based therapies or targeted pharmaceutical approaches. Some of these treatment options are beginning to move to human studies. Examples include antisense oligonucleotide treatment and stop codon suppression for Duchenne Muscular Dystrophy (DMD), myostatin inhibition in a range of muscular dystrophies, gene therapy approaches to DMD and pharmacological approaches to survival motor neuron gene (SMN) upregulation in Spinal Muscular Atrophy (SMA). These developments, while universally welcomed amongst scientists, clinicians and patient organisations, have exposed the lack of harmonisation of approaches to possibly beneficial therapeutics in NMD, which is hindering a smooth move into clinical trials.

TREAT-NMD is addressing this lack of harmonisation by creating a model in which the development of the tools of the Network through a long-term vision will bring delivery of new treatments while supporting optimal care for patients. The components of the TREAT-NMD model are illustrated in Figure 1. Individual partners (Table 1), working with international collaborators, are responsible for the delivery of each of these components of the network which address specific bottlenecks in therapy development and delivery including:

- the time taken for proper protocol design and lack of generally accepted outcome measures addressed via consensus meetings (1), regulatory engagement and a publicly available registry of outcome measures available through the TREAT-NMD website;

*Address for correspondence: Prof K. Bushby, Institute of Human Genetics, University of Newcastle, International Centre for Life, Central Parkway, Newcastle upon Tyne, NE1 3BZ, England. E-mail: www.treat-nmd.eu*

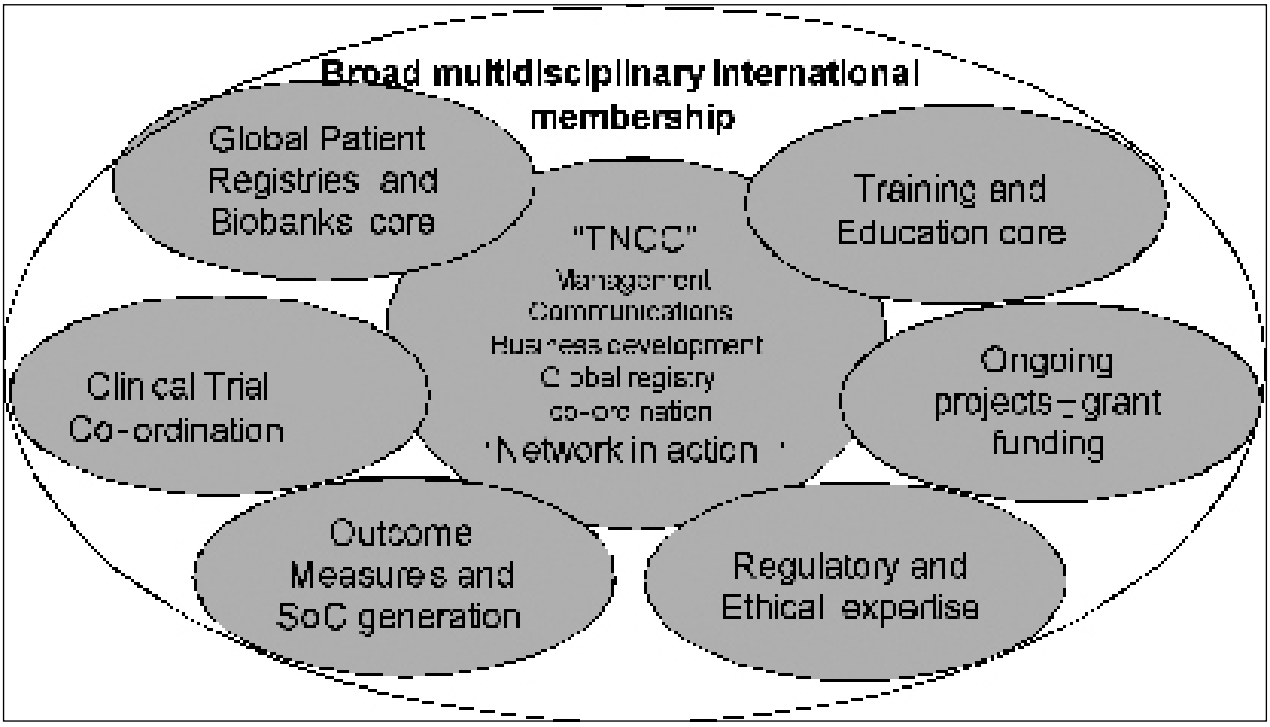


**Figure 1.** The TREAT-NMD network has worked to develop tools for trial readiness in a number of areas, and is also collaborating on additional research projects in the field.

**Table 1.** TREAT-NMD partners.

| |
|---|
| • University of Newcastle upon Tyne, UK (Project Coordinator) |
| • Institut National de la Santé et de la Recherche Médicale, France |
| • Leiden University Medical Center, The Netherlands |
| • Muskeldystrophie-Netzwerk e.V., Germany |
| • European Neuromuscular Centre, The Netherlands |
| • Summit PLC, UK |
| • Association Française contre les Myopathies and Institut de Myologie, France |
| • Biozentrum, University of Basel, Switzerland |
| • European Organisation for Rare Diseases, France |
| • Karolinska Institute, Sweden |
| • King's College London, UK |
| • Santhera Pharmaceuticals (Switzerland) LTD Liab.Co. |
| • Helsingin yliopisto, Finland |
| • Medical Research Council, UK |
| • Fondazione Telethon, Italy |
| • Université Catholique de Louvain, Belgium |
| • Universitat Autònoma de Barcelona, Spain |
| • GenoSafe SAS, France |
| • ACIES, France |
| • National Institute of Environmental Health, Hungary |
| • Genethon, France |
| • University College London, UK |

- lack of a number of appropriately trained sites with similar levels of standards of care and appropriate staff to run trials addressed via the establishment of the trial site registry;
- lack of knowledge about patient availability and characteristics addressed via the patient registries;
- better understanding of the interpretation of animal model experiments and prioritisation of drug candidates addressed by establishing an expert group to evaluate promising drug targets. This group (the TREAT-NMD advisory committee for therapeutics, TACT) will inform the community on the likely candidature of a molecule to move towards trials. The evaluation of the pre-clinical work has been developed by a group which has developed recommendations on the use of animal models in DMD (2) as well as standardised operating procedures for their assessment (in press).

## 2. Networking for optimal care and delivery of trials

As part of the TREAT-NMD project, the network has been working with international groups to generate and disseminate care standards for SMA and DMD. These collaborative projects have led to the publication of précis of care standards via the TREAT-NMD website in multiple languages. The TREAT-NMD care and trial site network offers a unique opportunity to develop international harmonisation to aid implementation of internationally agreed care standards and disseminate best practice Europe-wide. The Rare Diseases Task Force has noted the substantial national variation in implementation of care through expert centres in European countries and recognises the high added value of collaboration at a European level to harmonise access to expert care for patients across Europe. One method of implementing this is via the establishing of "European Reference Networks" for rare diseases. The public health ramifications of this strategy place it beyond TREAT-NMD's current remit as a translational research network; nonetheless, the infrastructure being established by TREAT-NMD makes it ideally placed to implement such a network for rare inherited neuromuscular disorders.

As part of its "trial-readiness" strategy, TREAT-NMD has been creating a registry of clinical sites across Europe (and beyond) which have expertise in neuromuscular disease or see neuromuscular patients. As of May 2009, the registry included detailed information on more than 150 clinical trial sites worldwide. In total, these sites can identify over 11,000 neuromuscular patients mapped to a set of diagnostic categories (currently DMD, SMA, CMD and LGMD). Mapping the location, expertise and patient cohorts of these clinical centres is proving key to finding sites capable of running upcoming clinical trials. However, this network of sites with neuromuscular expertise is not only valuable in terms of clinical trials, but also as a platform for disseminating best practice in patient care, for example:

- information on recent developments in the neuromuscular field, in particular outcome measures, systematic reviews, recent literature and trial results;
- up-to-date information on patient care;
- a forum for sharing expertise;
- access to shared tools and resources;
- training and education opportunities for PIs, clinicians and care staff;
- support in applying for funding opportunities;
- political/lobbying support;
- contacts to industry and other groups who are considering clinical trials;
- the opportunity to make use of the trial sites' infrastructure for trials and research arising within the network;
- a mechanism for evaluation and/or accreditation of centres as centres of expertise;
- links with accredited centres for genetic testing (collaborating with EuroGentest);
- links to existing key resources such as the TREAT-NMD global patient registries.

## 3. Patient registry development

One of the key TREAT-NMD infrastructures built up in the last 2 years is a global patient registry for DMD and SMA comprising more than 20 national patient registries worldwide. The DMD registries now hold more than 9,000 individual patient entries with standardized items and consent facilitating and accelerating clinical research and clinical trials while giving patients improved access to relevant information on standards of diagnosis and care.

Most innovative therapies for patients suffering from rare NMDs are expected to act on gene-specific molecular pathways. In some areas, the specific mutation will determine the applicability of a particular therapeutic technique. Therefore, patient registries for NMDs need to be gene-based and annotating each patient's mutation correctly is of high importance. Clinical information needs to be captured in a standardized way and updated regularly. For ease of use, and to respond to the need for regular updating, a core set of mandatory data are generated for each disorder. Participation of disease experts is essential for curation of genetic and clinical information

and adherence to the TREAT-NMD charter provides assurance of best practice in regulatory and ethical domains. Access to the data in the global registry is regulated by an international oversight committee.

TREAT-NMD is now working with other groups to support similar developments for other rare NMDs such as the Congenital Muscular Dystrophies (with Cure CMD) and Myotonic Dystrophy (with the Marigold Foundation), and others representing several genetic entities. For some of these disorders, leading scientists have set up local registries or private databases that may not be generally available to the research community, and may use different tools and practices (an inventory is available at www.treat-nmd.eu/registries/docs/rare_inventory.pdf). These experts were invited by ENMC and TREAT-NMD to participate in a workshop to encourage collaborative action towards gene-based patient registries for rare, inherited muscle disorders in Europe and worldwide.

The workshop concluded that harmonizing practices, joining forces and merging experience on gene-based patient registries may facilitate research into rare inherited muscle disorders, support upcoming clinical trials, and deliver standards of care (3). Several specific recommendations were made:

- to optimize resources, parallel developments for the same objectives/disorders (duplication) should be avoided;
- international harmonization of practices and data points should be achieved for each condition;
- information about the databases and registries as well as anonymized results should be made publicly available through the internet and other means;
- anonymized molecular and clinical data should be submitted to an already existing, open access locus-specific database;
- sustainability and long-term financing need to be considered from the outset of a patient registry/database. TREAT-NMD has developed a toolkit for patient organisations and professionals to assist setting up of registries for neuromuscular disorders (www.treat-nmd.eu/healthcare/patient-registries/toolkit).

## 4. Conclusions

TREAT-NMD is committed to delivering innovative treatments for rare neuromuscular diseases, starting with muscular dystrophies and spinal muscular atrophy, from laboratory development to clinical practice via the generation of a durable and sustainable network coordination centre. Although the roots of the network are within the EU 6th framework programme, the collaborations and work of the network now extends globally with members all across the world. Engagement with industry, patient groups and academia is growing with the realisation that the challenges of the new therapeutic era in NMD requires an increasing commitment to collaboration (4). More information on all aspects of the network, including how to become a member, and how to contribute to its activities can be found at www.treat-nmd.eu.

## References

1. Mercuri E, Mayhew A, Muntoni F, et al. TREAT-NMD Neuromuscular Network. Towards harmonisation of outcome measures for DMD and SMA within TREAT-NMD; report of three expert workshops: TREAT-NMD/ENMC workshop on outcome measures, 12th-13th May 2007, Naarden, The Netherlands; TREAT-NMD workshop on outcome measures in experimental trials for DMD, 30th June-1st July 2007, Naarden, The Netherlands; conjoint Institute of Myology TREAT-NMD meeting on physical activity monitoring in neuromuscular disorders, 11th July 2007, Paris, France. Neuromuscul Disord 2008;18:894-903.
2. Willmann R, Possekel S, Dubach-Powell J, et al. Mammalian animal models for Duchenne muscular dystrophy. Neuromuscul Disord 2009;19:241-9.
3. Sárközy A, Bushby K, Béroud C, et al. 157th ENMC International Workshop: patient registries for rare, inherited muscular disorders 25-27 January 2008, Naarden, The Netherlands. Neuromuscul Disord 2008;18:997-1001.
4. Butcher J. Cooperation is key, say neuromuscular-disease researchers. Lancet Neurol 2007;6:298-9.